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(54) **QUINAZOLINE DERIVATIVES FOR THE TREATMENT OF CANCER DISEASES**

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CPC A61K 31/517; A61K 31/553

See application file for complete search history.

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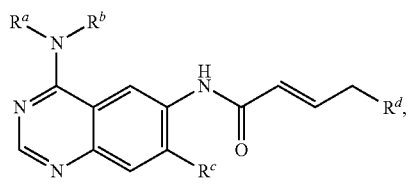
(57) **ABSTRACT**

The present invention relates to the use of quinazolines of formula (I),



(I)

wherein the groups R^a to R^d have the meanings given in the claims and specification, in cancer therapy.

5 Claims, 4 Drawing Sheets

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Figure 1: BIBW 2992 induces apoptosis in NCI-N87 gastric cancer cells

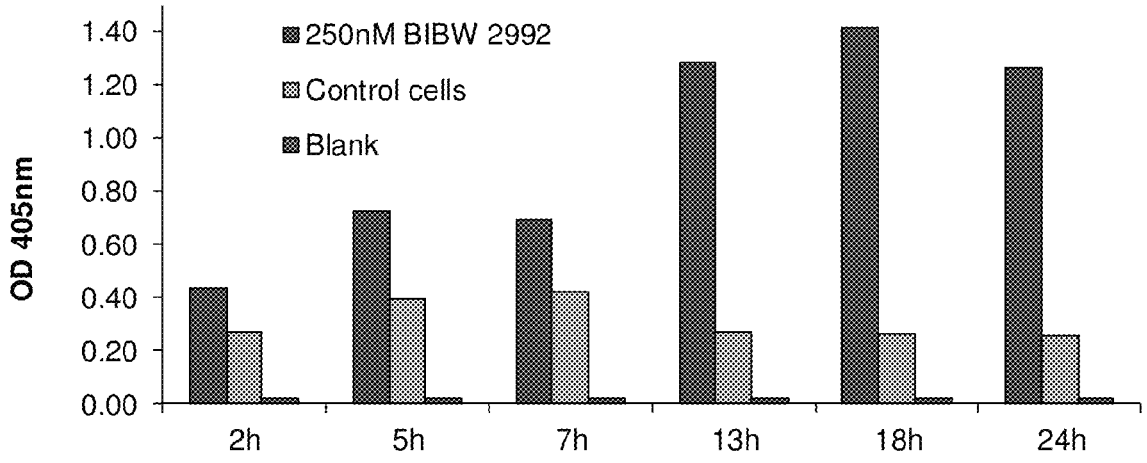


Figure 2: Effect of BIBW 2992 on the growth of preexisting HNSCC FaDu xenografts

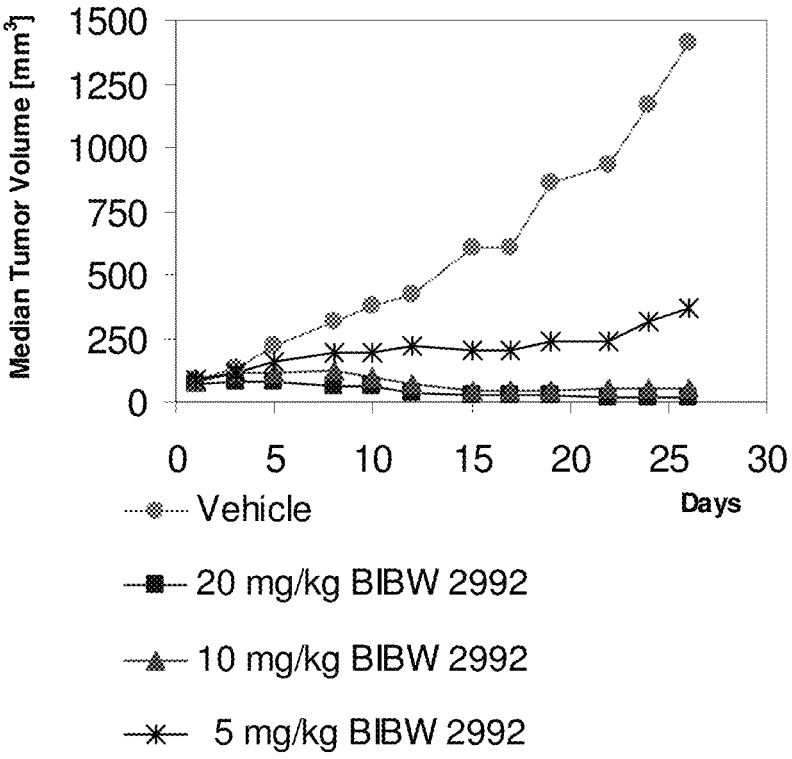
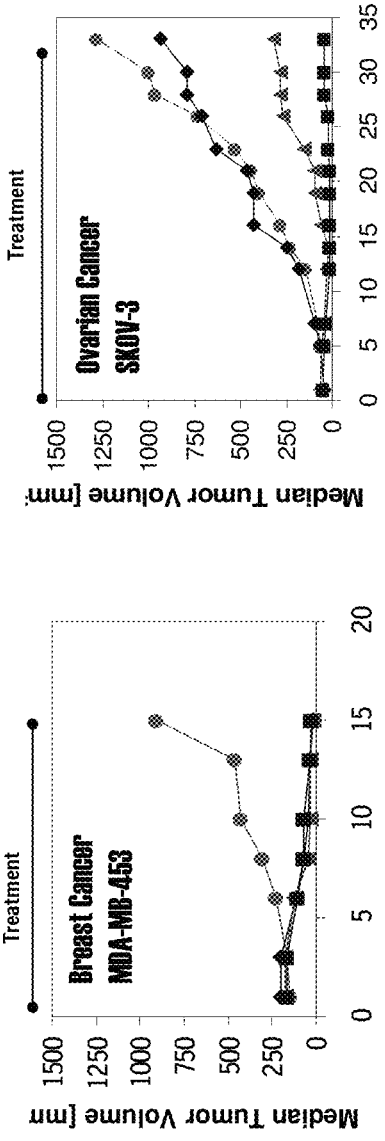


Figure 3: Effect of BIBW 2992 on the growth of MDA-MB-453 and SKOV-3 xenografts



compound	gefitinib	canertinib	BIBW 2992
Cmax [nM]	4181	674	83
$AUC_{(0\text{-}24h)}$ [nM*h]	41934	5066	972

compound	gefitinib	canertinib	BIBW 2992
Cmax [nM]	4737	359	236
$AUC_{(0\text{-}24h)}$ [nM*h]	62490	2803	2156

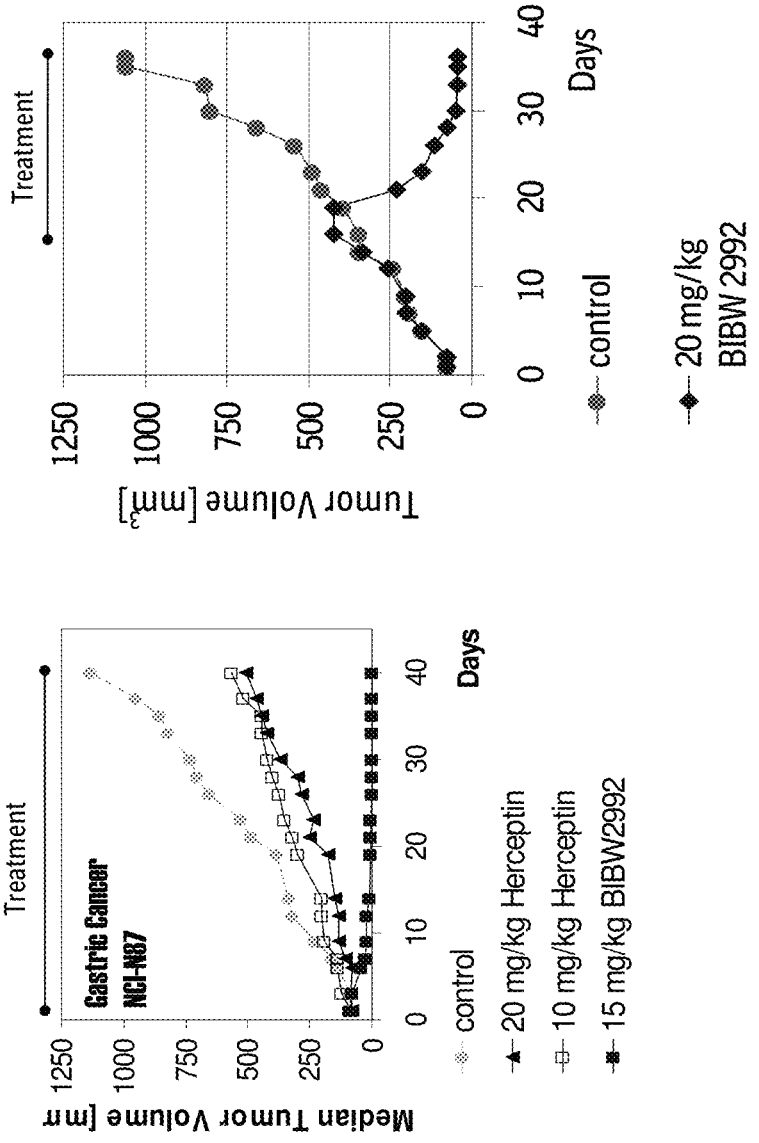
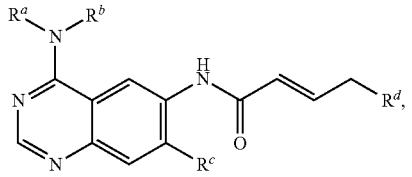


Figure 4: Effect of BIBW 2992 on the growth of MDA-MB-453 and SKOV-3 xenografts

QUINAZOLINE DERIVATIVES FOR THE TREATMENT OF CANCER DISEASES

The present invention relates to the use of quinazolines of formula (I),



(I)

wherein the groups R^a to R^d have the meanings given in the claims and specification, in cancer therapy.

BACKGROUND OF THE INVENTION

Compounds of formula (I) are disclosed in WO 02/50043, WO 2004/074263 and WO 2005/037824 as dual inhibitors of erbb1 receptor (EGFR) and erbB2 (Her2/neu) receptor tyrosine kinases, suitable for the treatment of e.g. benign or malignant tumours, particularly tumours of epithelial and neuroepithelial origin, metastasisation and the abnormal proliferation of vascular endothelial cells (neoangiogenesis), for treating diseases of the airways and lungs which are accompanied by increased or altered production of mucus caused by stimulation by tyrosine kinases, as well as for treating diseases of the gastrointestinal tract and bile duct and gall bladder which are associated with disrupted activity of the tyrosine kinases. The disclosure of WO 02/50043, WO 2004/074263 and WO 2005/037824 includes preparation as well as pharmaceutical formulations of the compounds and is incorporated by reference regarding these aspects. Furthermore, it is known for treatment of tumour diseases that the compounds may be used in monotherapy or in conjunction with other anti-tumour therapeutic agents, for example in combination with topoisomerase inhibitors (e.g. etoposide), mitosis inhibitors (e.g. vinblastine), compounds which interact with nucleic acids (e.g. cis-platin, cyclophosphamide, adriamycin), hormone antagonists (e.g. tamoxifen), inhibitors of metabolic processes (e.g. 5-FU etc.), cytokines (e.g. interferons) or antibodies.

SUMMARY OF THE INVENTION

It has been found that the compounds of formula (I) provide unexpected advantages in the treatment of cancer, e.g. superior efficacy and/or reduced side effects, especially in the treatment of several specific cancer-subindications.

A first aspect of the present invention therefore is a method of treating cancer, preferably the specific cancer-subindications referred to hereinafter, said method comprising administering a therapeutically effective amount of a compound of formula (I) to a patient in need thereof, optionally in combination with radiotherapy, radio-immunotherapy and/or tumour resection by surgery.

Any reference to a compound of formula (I) in connection with the invention should be understood to include the tautomers, racemates, enantiomers and diastereomers thereof, if any, the mixtures thereof as well as the pharmacologically acceptable acid addition salts, solvates, hydrates, polymorphs, physiologically functional derivatives or prodrugs thereof.

The expression "patient" relates to a human or non-human mammalian patient suffering from cancer and thus in need of such treatment, preferably the patient is a human person. Furthermore, the expression "patient" should be understood to include such cancer patients carrying tumors with wild-type EGF receptor as well as pre-selected cancer patients

with tumors harboring activating EGFR mutations. These can be located in the tyrosine kinase domain of the EGF receptor such as for instance the L858R or L861 point mutations in the activation loop (exon 21), or in-frame deletion/insertion mutations in the ELREA sequence (exon 19), or substitutions in G719 situated in the nucleotide binding loop (exon 18). Additional activating mutations have been reported in the extracellular domain of the EGF receptor in various indications (e.g. EGFR vIII displaying exon 2-7 deletions). Other mutations such as the T790M point mutation in exon 20 as well as certain exon 20 insertions (e.g. D770_N771insNPG) which confer resistance to particular drugs should also be included, as well as double mutants such as the combined L858R/T790M mutation or the exon-19-del/T790M.

The expression "patient" should be understood to include also such cancer patients carrying tumors with wild-type HER2 receptor as well as pre-selected cancer patients with tumors harboring activating HER2 mutations, e.g. M774_A775insAYVM.

The indication "cancer" as used in the context of the invention is to be understood in a most general sense as a disease characterized by inappropriate cellular proliferation, migration, apoptosis or angiogenesis, preferably by inappropriate cellular proliferation. Inappropriate cell proliferation means cellular proliferation resulting from inappropriate cell growth, from excessive cell division, from cell division at an accelerated rate and/or from inappropriate cell survival.

"Radiotherapy" means administering ionizing radiation to the patient, as conventionally used in cancer therapy. Radiotherapy may be applied before, in parallel or after treatment by administration of a compound of formula (I).

"Tumour resection by surgery" is one standard option in cancer therapy and may be applied before or after treatment by administration of a compound of formula (I).

A second aspect of the present invention is directed to the use of a compound of formula (I) for the manufacture of a medicament for the treatment of cancer, preferably for the treatment of the specific cancer-subindications referred to hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**: shows BIBW 2992 induces apoptosis in NCI-N87 gastric cancer cells.

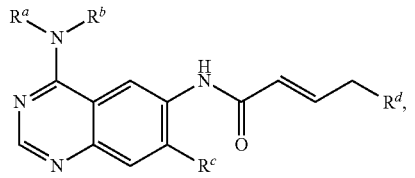
FIG. **2**: shows the effect of BIBW 2992 on the growth of preexisting HNSCC FaDu xenografts.

FIG. **3**: shows the effect of BIBW 2992 on the growth of MDA-MB-453 and SKOV-3 xenografts.

FIG. **4**: shows the effect of BIBW 2992 on the growth of MDA-MB-453 and SKOV-3 xenografts.

DETAILED DESCRIPTION OF THE INVENTION

In a first embodiment (1), both with regard to the first and second aspect of the invention, formula (I)



(I)

is defined to encompass those compounds wherein

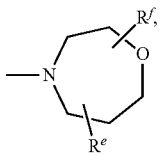
R^a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group,

R^b denotes a hydrogen atom or a C_{1-4}-alkyl group,

R^c denotes a cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy, tetrahydrofuran-3-yl-oxy, tetrahydrofuran-2-yl-methoxy, tetrahydrofuran-3-yl-methoxy, tetrahydropyran-4-yl-oxy or tetrahydropyran-4-yl-methoxy group,

R^d denotes a dimethylamino, N-cyclopropyl-N-methyl-amino, N-cyclopropylmethyl-N-methyl-amino, N-ethyl-N-methyl-amino, N,N-diethylamino, N-isopropyl-N-methyl-amino, N-(2-methoxyethyl)-N-methyl-amino, N-(1-methoxy-2-propyl)-N-methyl-amino, N-(3-methoxypropyl)-N-methyl-amino, pyrrolidino, 2-methylpyrrolidino, 2-(methoxymethyl)-pyrrolidino, morpholino, (1S,4S)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl, (1R,4R)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl, N-cyclopropyl-N-methyl-amino-, N-methyl-N-(tetrahydrofuran-3-yl)-amino, N-methyl-N-(tetrahydrofuran-2-ylmethyl)-amino, N-methyl-N-(tetrahydrofuran-3-yl-methyl)-amino, N-methyl-N(tetrahydropyran-4-yl)-amino or N-methyl-N-(tetrahydropyran-4-yl-methyl)-amino group, or a group of formula (II)

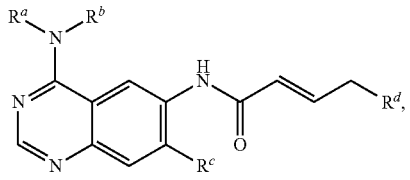
(II)



wherein R^e and R^f, which may be identical or different, in each case denote a hydrogen atom or a C_{1-3}-alkyl group, optionally in form of its tautomers, racemates, enantiomers, diastereomers and the mixtures thereof and optionally in form of the pharmacologically acceptable acid addition salts, solvates, hydrates, polymorphs, physiologically functional derivatives or prodrugs thereof.

In a second embodiment (2), both with regard to the first and second aspect of the invention, formula (I)

(I)



is defined to encompass those compounds wherein

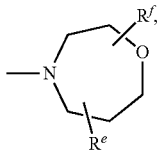
R^a denotes a 3-chloro-4-fluorophenyl group,

R^b denotes a hydrogen atom,

R^c denotes a cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy, tetrahydrofuran-3-yl-oxy, tetrahydrofuran-2-yl-methoxy, tetrahydrofuran-3-yl-methoxy, tetrahydropyran-4-yl-oxy or tetrahydropyran-4-yl-methoxy group,

R^d denotes a dimethylamino, N-cyclopropyl-N-methyl-amino, N-cyclopropylmethyl-N-methyl-amino, N-ethyl-N-methyl-amino, N,N-diethylamino, N-isopropyl-N-methyl-amino, N-(2-methoxyethyl)-N-methyl-amino, N-(1-methoxy-2-propyl)-N-methyl-amino, N-(3-methoxypropyl)-N-methyl-amino, pyrrolidino, 2-methylpyrrolidino, 2-(methoxymethyl)-pyrrolidino, morpholino, (1S,4S)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl, (1R,4R)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl, N-methyl-N-(tetrahydrofuran-3-yl)-amino, N-methyl-N-(tetrahydrofuran-2-yl-methyl)-amino, N-methyl-N-(tetrahydrofuran-3-yl-methyl)-amino, N-methyl-N-(tetrahydropyran-4-yl)-amino or N-methyl-N-(tetrahydropyran-4-yl-methyl)-amino group, or a group of formula (II)

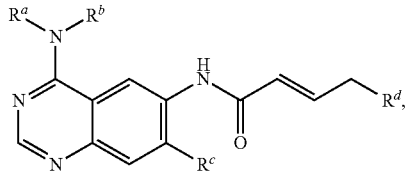
(II)



wherein R^e and R^f denote a hydrogen atom.

In a third embodiment (3), both with regard to the first and second aspect of the invention, formula (I)

(I)



is defined to encompass those compounds wherein

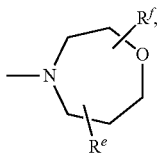
R^a denotes a 3-chloro-4-fluorophenyl group,

R^b denotes a hydrogen atom,

R^c denotes a tetrahydrofuran-3-yl-oxy, tetrahydrofuran-2-yl-methoxy, tetrahydrofuran-3-yl-methoxy, tetrahydropyran-4-yl-oxy or tetrahydropyran-4-yl-methoxy group,

R^d denotes a dimethylamino, N-cyclopropyl-N-methyl, N-ethyl-N-methyl-amino, N,N-diethylamino, N-isopropyl-N-methyl-amino, morpholino, (1S,4S)-2-oxa-5-aza-bicyclo-[2.2.1]hept-5-yl or (1R,4R)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl, group, or a group of formula (II)

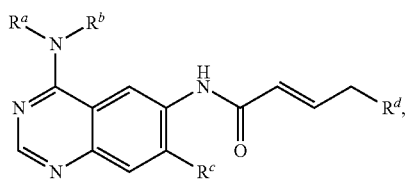
(II)



wherein R^e and R^f denote a hydrogen atom.

In a fourth embodiment (4), both with regard to the first and second aspect of the invention, formula (I)

(I)



is defined to encompass those compounds wherein

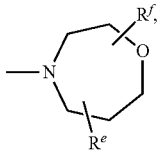
R^a denotes a 3-chloro-4-fluorophenyl group,

R^b denotes a hydrogen atom,

R^c denotes a tetrahydrofuran-3-yl-oxy, tetrahydrofuran-2-yl-methoxy or tetrahydrofuran-3-yl-methoxy group,

R^d denotes a dimethylamino group or a group of formula (II)

(II)



wherein R^e and R^f, denote a hydrogen atom.

In a fifth embodiment (5), both with regard to the first and second aspect of the invention, formula (I) is defined to encompass the compounds selected from the group consisting of

(a) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline,

(b) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline,

(c) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline,

(d) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline,

(e) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-(tetrahydropyran-4-yloxy)-quinazoline,

(f) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline,

(g) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-3-yl)methoxy]-quinazoline,

(h) 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropyl-methoxy-quinazoline,

(i) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline,

(j) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline,

(k) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(homomorpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline,

(l) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(N-ethyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline,

(m) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(N-isopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline,

(n) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline,

(o) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(N,N-diethyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropyl-methoxy-quinazoline,

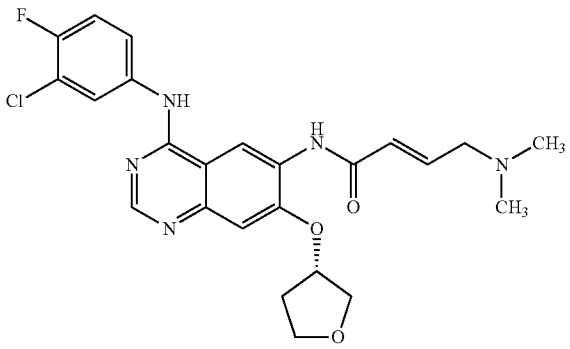
(p) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((1S,4S)-2-oxa-5-aza-bicyclo[2.2.1]-hept-5-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline,

(q) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((1R,4R)-2-oxa-5-aza-bicyclo[2.2.1]-hept-5-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline and

(r) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropyl-methoxy-quinazoline.

In a sixth embodiment (6), both with regard to the first and second aspect of the invention, the compounds of formula (I) are selected from the group consisting of

(d) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline,



(k) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(homomorpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline,

the dimaleate salt of compound (d) being especially preferred:

(d') 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate.

In a preferred embodiment the invention relates to the use of a compound of formula (I) according to the invention, wherein the disease is cancer selected from the group consisting of carcinomas, sarcomas, melanomas, myelomas, hematological neoplasias, lymphomas and childhood cancers.

Examples of carcinomas within the scope of the invention include but are not limited to adenocarcinoma (AC), squamous cell carcinoma (SCC) and mixed or undifferentiated carcinomas. Carcinomas within the scope of the invention include but are not limited to the following histologies:

- Head and neck tumours: SCC, AC, transitional cell cancers, mucoepidermoid cancers, undifferentiated carcinomas;
- Central nervous system tumours: Astrocytoma, glioblastoma, meningeoma, neurinoma, schwannoma, ependymoma, hypophysoma, oligodendroglioma, medulloblastoma;
- Bronchial and mediastinal tumours:
  - Bronchial tumours:
    - Small cell lung cancers (SCLC): oat-cell lung cancer, intermediate cell cancer, combined oat-cell lung cancer;
    - Non-small cell lung cancers (NSCLC): SCC, spindle cell carcinoma, AC, bronchioalveolar carcinoma, large cell NSCLC, clear cell NSCLC;
  - Mesothelioma;
  - Thymoma;

Thyroid carcinomas: papillary, follicular, anaplastic, medullary;

Tumours of the gastrointestinal tract:

Oesophageal cancers: SCC, AC, anaplastic, carcinoid, sarcoma;

Gastric cancers: AC, adenosquamous, anaplastic;

Colorectal cancers: AC, including hereditary forms of AC, carcinoid, sarcoma;

Anal cancers: SCC, transitional epithelial cancer, AC, basal cell carcinoma;

Pancreatic cancers: AC, including ductal and acinary cancers, papillary, adenosquamous, undifferentiated, tumours of the endocrine pancreas;

Hepatocellular carcinoma, cholangiocarcinoma, angiosarcoma, hepatoblastoma;

Biliary carcinomas: AC, SCC, small cell, undifferentiated;

Gastrointestinal stroma tumours (GIST);

Gynaecological cancers:

Breast cancers: AC, including invasive ductal, lobular and medullary cancers, tubular, mucinous cancers, Paget-carcinoma, inflammatory carcinoma, ductal and lobular carcinoma in situ;

Ovarian cancers: Epithelial tumours, stroma tumours, germ cell tumours, undifferentiated tumours;

Cervical cancers: SCC, AC, mixed and undifferentiated tumours;

Endometrial cancers: AC, SCC, mixed, undifferentiated tumours;

Vulvar cancers: SCC, AC;

Vaginal cancers: SCC, AC;

Urinary tract and testicular cancers:

Testicular cancers: seminoma;

Non-seminomatous germ cell tumours: teratoma, embryonal cell carcinoma, choriocarcinoma, yolk sac tumour, mixed, Sertoli and Leydig-cell tumours;

Extragonadal germ cell tumours;

Prostate cancers: AC, small cell, SCC;

Renal cell cancers: AC, including clear cell, papillary and chromophobous carcinomas, hereditary forms (e.g. von-Hippel-Lindau syndrome), nephroblastoma;

Urinary bladder cancers: transitional cell (urothelial) cancers, SCC, AC;

Urethral cancers: SCC, transitional cell cancers, AC;

Penile cancers: SCC;

Tumours of endocrine tissue:

Thyroid cancers: papillary, follicular, anaplastic, medullary carcinomas, including MEN syndrome;

Tumours of the endocrine pancreas;

Carcinoids;

Pheochromocytoma.

Examples of sarcomas within the scope of the invention include but are not limited to Ewing-sarcoma, osteosarcoma or osteogenic sarcoma, chondrosarcoma, synovial sarcoma, leiomyosarcoma, rhabdomyosarcoma, mesothelial sarcoma or mesothelioma, fibrosarcoma, angiosarcoma or hemangioendothelioma, liposarcoma, glioma or astrocytoma, myxosarcoma, malignant fibrous histiocytoma, mesenchymous or mixed mesodermal tumour, neuroblastoma and clear cell sarcoma.

Examples of melanomas within the scope of the invention include but are not limited to superficial spreading melanoma, nodular and lentigo-maligna melanoma.

Examples of myelomas within the scope of the invention include but are not limited to immunocytoma, plasmocytoma and multiple myeloma.

In another preferred embodiment the invention relates to the use according to the invention, wherein the hematological neoplasia is leukemia.

Further examples of hematologic neoplasias within the scope of the invention include but are not limited to acute or chronic leukemias of myeloid, erythroid or lymphatic origin, myelodysplastic syndromes (MDS) and myeloproliferative syndromes (MPS, such as chronic myelogeneous leukemia, osteomyelofibrosis, polycythemia vera or essential thrombocythemia).

Examples of lymphomas within the scope of the invention include but are not limited to:

Hodgkin's-lymphoma;

Non-Hodgkin's-lymphomas: T- and B-cell lymphomas

B-cell lymphomas:

Low and intermediate grade: Chronic lymphocytic leukemia (CLL), prolymphocytic leukemia (PLL), small lymphocytic lymphoma, hairy cell leukemia, plasmacytoid lymphoma, mantle cell lymphoma, follicular lymphoma, marginal zone lymphoma including MALT-lymphoma;

High grade: diffuse large B-cell lymphoma (DLBCL including immunoblastic and centroblastic variants), lymphoblastic, Burkitt's lymphoma;

T-cell lymphomas:

Low grade: T-CLL, T-PLL, Mycosis fungoides, Sezary-syndrome;

High grade: Anaplastic large cell, T-immunoblastic and lymphoblastic.

In another preferred embodiment the invention relates to the use according to the invention, wherein the disease is cancer selected from the group consisting of mixed tumours, undifferentiated tumours and metastases thereof.

Examples of mixed tumours within the scope of the invention include but are not limited to adenosquamous carcinomas, mixed mesodermal tumours, carcinosarcomas and teratocarcinomas.

Examples of undifferentiated, other tumours or metastases thereof within the scope of the invention include but are not limited to undifferentiated tumours, carcinomas of unknown primary (CUP), metastases of unknown primary (MUP) and pheochromocytoma, carcinoids.

Additionally the following tumour diseases which can be treated with a compound of formula (I) in accordance with the invention are summarized:

acral lentiginous melanoma, actinic keratoses, adenoid cycstic carcinoma, adenomas, adenosarcoma, adrenocortical carcinoma, AIDS-related lymphoma, bartholin gland carcinoma, brain stem glioma, capillary carcinoma, central nervous system lymphoma, chondosarcoma, choriod plexus papilloma/carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, epitheloid, focal nodular hyperplasia, gastrinoma, gestational trophoblastic tumor, glucagonoma, hepatic adenoma, hepatic adenomatosis, hypopharyngeal cancer, hypothalamic and visual pathway glioma, insulinoma, intraepithelial neoplasia, interepithelial squamous cell neoplasia, intraocular invasive squamous cell carcinoma, large cell carcinoma, islet cell carcinoma, Kaposi's sarcoma, laryngeal cancer, leukemia-related disorders, lip and oral cavity cancer, malignant mesothelial tumors, malignant thymoma, medulloepithelioma, merkel cell carcinoma, mucoepidermoid carcinoma, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndrome, myeloproliferative disorders, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroepithelial adenocarcinoma, nodular

melanoma, oat cell carcinoma, oligodendroglial, oral cancer, oropharyngeal cancer, pineal cell, pituitary tumors, pseudosarcoma, pulmonary blastoma, parathyroid cancer, pineal and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm, pleuropulmonary blastoma, retinoblastoma, serous carcinoma, small intestine cancer, soft tissue carcinomas, somatostatin-secreting tumor, supratentorial primitive neuroectodermal tumors, uveal melanoma, verrucous carcinoma, vipoma, Waldenstrom's macroglobulinemia, well differentiated carcinoma, and Wilm's tumor.

In a further preferred embodiment (7), both with regard to the first and second aspect of the invention, the compounds of formula (I) are selected from the group consisting of

(a) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline,

(b) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline,

(c) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline,

(d) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline (BIBW2992),

(e) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-(tetrahydropyran-4-yloxy)-quinazoline,

(f) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline,

(g) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-3-yl)methoxy]-quinazoline,

(h) 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

(i) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline,

(j) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline,

(k) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(homomorpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, and

(r) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

and the cancer indication to be treated by administration of a compound of formula (I) is selected from the group consisting of

- Head and neck tumours: SCC, AC, transitional cell cancers, mucoepidermoid cancers, undifferentiated carcinomas;
- Central nervous system tumours: Astrocytoma, glioblastoma, meningeoma, neurinoma, schwannoma, ependymoma, hypophysoma, oligodendroglioma, medulloblastoma;
- Bronchial and mediastinal tumours:
  - Bronchial tumours:
    - Non-small cell lung cancers (NSCLC): SCC, spindle cell carcinoma, AC, bronchioalveolar carcinoma, large cell NSCLC, clear cell NSCLC;
  - Thyroid carcinomas: papillary, follicular, anaplastic, medullary;
- Tumours of the gastrointestinal tract:
  - Oesophageal cancers: SCC, AC, anaplastic;
  - Gastric cancers: AC, adenosquamous, anaplastic;
  - Colorectal cancers: AC, including hereditary forms of AC, carcinoid, sarcoma;
  - Pancreatic cancers: AC, including ductal and acinary cancers, papillary, adenosquamous, undifferentiated, tumours of the endocrine pancreas;
  - Hepatocellular cancers, cholangiocarcinoma
- Gynaecological cancers:
  - Breast cancers: AC, including invasive ductal, lobular and medullary cancers, tubular, mucinous cancers, Paget-carcinoma, inflammatory carcinoma, ductal and lobular carcinoma in situ;
  - Ovarian cancers: Epithelial tumours, stroma tumours, germ cell tumours, undifferentiated tumours;
- Urinary tract and testicular cancers:
  - Prostate cancers: AC, small cell, SCC;
  - Renal cell cancers: AC, including clear cell, papillary and chromophobous carcinomas, hereditary forms (e.g. von-Hippel-Lindau syndrome), Wilm's tumor, nephroblastoma;
  - Urinary bladder cancers: transitional cell (urothelial) cancers, SCC, AC.

Examples of sarcomas within the scope of the invention include but are not limited to Ewing-sarcoma, osteosarcoma or osteogenic sarcoma, chondrosarcoma, synovial sarcoma, leiomyosarcoma, rhabdomyosarcoma, mesothelial sarcoma or mesothelioma, fibrosarcoma, angiosarcoma or hemangioendothelioma, liposarcoma, glioma or astrocytoma, myxosarcoma, malignant fibrous histiocytoma, mesenchymous or mixed mesodermal tumour, neuroblastoma and clear cell sarcoma.

In a very preferred embodiment (8), both with regard to the first and second aspect of the invention, the compounds of formula (I) are selected from the group consisting of

(d) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline (BIBW2992),

(k) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(homomorpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline,

the dimaleate salt of compound (d) being especially preferred:

(d') 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate (BIBW2992 MA_2),

and the cancer indication to be treated by administration of a compound of formula (I) is selected from the group consisting of

- Head and neck tumours: SCC, AC, transitional cell cancers, mucoepidermoid cancers, undifferentiated carcinomas;
- Colorectal cancers, metastatic or non-metastatic: AC, including hereditary forms of AC, carcinoid, sarcoma;
- Pancreatic cancers: AC, including ductal and acinary cancers, papillary, adenosquamous, undifferentiated, tumours of the endocrine pancreas;
- Breast cancers, metastatic or non-metastatic: AC, including invasive ductal, lobular and medullary cancers, tubular, mucinous cancers, Paget-carcinoma, inflammatory carcinoma, ductal and lobular carcinoma in situ;
- Prostate cancers: AC, small cell, SCC;
- Gastric cancers: AC, adenosquamous, anaplastic;
- Ovarian cancer;

Non-small cell lung cancers (NSCLC): SCC, spindle cell carcinoma, AC, bronchioalveolar carcinoma, large cell NSCLC, clear cell NSCLC.

It is known that cancer patients carrying activating EGFR mutations in their tumors, i.e. within the tyrosine kinase domain of the EGF receptor, may show increased sensitivity to treatment with EGFR inhibitors. Analogously, cancer patients carrying activating HER2 mutations, e.g. M774_A775insAYVM, in their tumors may show increased sensitivity to treatment with HER2 inhibitors. Both groups of patients as well as a subgroup carrying both activating EGFR and HER2 mutations may show increased sensitivity to treatment with dual inhibitors of erbb1 receptor (EGFR) and erbB2 (Her2/neu).

The presence of specific gain-of-function mutations within the tyrosine kinase domain of the EGF receptor in a subgroup of NSCLC patients has been associated with increased sensitivity to treatment with gefitinib and erlotinib (Lynch, New England Journal Medicine 350, 2129 (2004); Paez, Science 304, 1497 (2004); Pao, Proceedings of the National Academy of Science of the United States 101, 13306 (2004)). In particular, the L858R point mutation (exon 21) as well as deletion/insertion mutations in the ELREA sequence (exon 19) account for the majority of gefitinib responders. A secondary point mutation in exon 20, T790M, is associated with acquired resistance to gefitinib or erlotinib. This mutation is analogous to the T315I mutation identified in CML patients who relapse under imatinib treatment (imatinib resistant patients).

Irreversible inhibitors (e.g., HKI-272 or CL 387,785), in contrast to reversible inhibitors (e.g., gefitinib), are able to inhibit proliferation and EGF-induced EGFR phosphorylation in cell lines expressing double mutant EGF receptors (Kwak, Proceedings of the National Academy of Science of the United States 102, 7665 (2005) and Kobayashi, New England Journal Medicine 352, 786 (2005)).

Any aspect of the present invention therefore includes, as a sub-aspect, optional pre-selection of cancer patients for an EGFR mutation in the tyrosine kinase domain of the EGF receptor as well as pre-selection of cancer patients for an HER2 mutation. The EGFR mutations preferably relevant in in this context are selected from the group consisting of the L858R and L861 point mutations in the activation loop (exon 21), in-frame deletion/insertion mutations in the ELREA sequence (exon 19), substitutions in G719 situated in the nucleotide binding loop (exon 18), activating mutations in the extracellular domain of the EGF receptor such as EGFR vIII displaying exon 2-7 deletions, the T790M point mutation in exon 20, exon 20 insertions such as D770_N771insNPG, and double mutants such as the combined L858R/T790M mutation and the exon-19-del/T790M. The HER2 mutation preferably relevant in in this context is the M774_A775insAYVM mutation.

Methods for detecting mutations in the tyrosine kinase domain of the EGF receptor are known in the art, several corresponding diagnostic tools are approved by the FDA and commercially available, e.g. an assay for the detection of epidermal growth factor receptor mutations in patients with non-small cell lung cancer (Genzyme Corp.; see also Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 24, No 18S (June 20 Supplement), 2006: Abstract 10060).

Any of the embodiments of the invention mentioned hereinbefore defining compounds of formula (I) and cancer indications applies accordingly to the optional sub-aspect of pre-selection of cancer patients for an activating EGFR mutation in the tyrosine kinase domain of the EGF receptor and/or pre-selection of cancer patients for an activating HER2 mutation. Treatment of EGFR mutant cancer patients with the compounds of formula (I) may allow a response in cancer patients with acquired or persistent resistance to gefitinib or erlotinib treatment. Treatment of cancer patients carrying an activating HER2 mutant in their tumors with the compounds of formula (I) may allow a responce in cancer patients with acquired or persistent resistance to certain chemotherapeutics such as e.g. lapatinib or herceptin.

Most preferred cancer indications with EGFR or HER2 mutations relevant in connection with the sub-aspect of patient pre-selection for mutations are selected from the group consisting of

Head and neck tumours: SCC, AC, transitional cell cancers, mucoepidermoid cancers, undifferentiated carcinomas;

Colorectal cancers, metastatic or non-metastatic: AC, including hereditary forms of AC, carcinoid, sarcoma;

Pancreatic cancers: AC, including ductal and acinary cancers, papillary, adenosquamous, undifferentiated, tumours of the endocrine pancreas;

Breast cancers, metastatic or non-metastatic: AC, including invasive ductal, lobular and medullary cancers, tubular, mucinous cancers, Paget-carcinoma, inflammatory carcinoma, ductal and lobular carcinoma in situ;

Prostate cancers: AC, small cell, SCC;

Gastric cancers: AC, adenosquamous, anaplastic;

Ovarian cancer;

Non-small cell lung cancers (NSCLC): SCC, spindle cell carcinoma, AC, bronchioalveolar carcinoma, large cell NSCLC, clear cell NSCLC,

but especially

Non-small cell lung cancers (NSCLC): SCC, spindle cell carcinoma, AC, bronchioalveolar carcinoma, large cell NSCLC, clear cell NSCLC, especially metastatic, second line patients who have failed at least one prior chemotherapy regimen or 3rd/4th line patients who have received Tarceva or Iressa for at least 12 weeks and then failed,

preferably to be treated by administration of a compound of formula (I) selected from the group consisting of:

(a) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline,

(b) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline,

(c) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline,

(d) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline (BIBW2992),

(e) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-(tetrahydropyran-4-yloxy)-quinazoline,

(f) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline,

(g) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-3-yl)methoxy]-quinazoline,

(h) 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

(i) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline,

(j) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline,

(k) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(homomorpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, and

(r) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

or a pharmaceutically acceptable salt thereof.

The first aspect of the present invention therefore includes, as a sub-aspect (A), a method of treating cancer comprising pre-selection of cancer patients for EGFR and/or HER2 mutations and administering a therapeutically effective amount of a compound of formula (I) to a pre-selected cancer patient shown to carry an EGFR mutation in the tyrosine kinase domain of the EGF receptor and/or with a tumor harboring an activating HER2 mutation, optionally in combination with radiotherapy, radio-immunotherapy and/or tumour resection by surgery.

Accordingly, the second aspect of the present invention includes, as a sub-aspect (B), the use of a compound of formula (I) for the manufacture of a medicament for the treatment of cancer in a pre-selected cancer patient shown to carry an EGFR mutation in the tyrosine kinase domain of the EGF receptor and/or with a tumor harboring an activating HER2 mutation.

Method of Treatment:

The method of treatment according to the invention comprises administration of a therapeutically effective amount of a compound of formula (I), optionally in form of its tautomers, racemates, enantiomers, diastereomers and the mixtures thereof and optionally in form of the pharmacologically acceptable acid addition salts, solvates, hydrates, polymorphs or physiologically functional derivatives thereof, to a patient in need thereof, wherein the active ingredient is administered orally, enterically, transdermally, intravenously, peritoneally or by injection, preferably orally. The patient preferably is a human patient.

Dosage:

The compounds of formula (I) may be administered to the human patient in a daily dose of 0.01-4 mg/kg of body weight (bw), preferably 0.1-2 mg/kg, particularly preferred in a dose of 0.2-1.3 mg/kg bw. For oral treatment the compounds of formula (I) may be administered daily in a total dose of 10, 20, 30, 40, 50, 60, 70, 100, 200, or 300 mg, optionally divided into multiple doses, e.g. 1 to 3 doses to be administered through the day. Preferably the oral daily dose is administered only once a time. These doses can be applied with any of the compounds of formula (I), e.g. with BIBW2992 or an equivalent dose of BIBW2992MA$_2$ containing respective amounts of the active base component. Especially for higher doses periods of treatment should alternate with periods of recovery, without administering the active of formula (I). For instance, treatment could follow a "7 day on-7 day off", a "14 day on-14 day off", a "21 day on 7 day off" or a continuous dosing schedule. "On-off" time periods can be chosen shorter, especially if higher doses are administered, or individually adapted to the needs of the patient. The dosage for intravenous use of a compound of formula (I), e.g. of BIBW2992MA$_2$ may be 1-1000 mg, preferably 5-300 mg, particularly preferred 10-100 mg (dosages refer to the base form BIBW2992), either given as a bolus or, especially if higher doses are applied, as a slow intravenous infusion over several hours, e.g. over about 1, 2, 4, 6, 10, 12 or 24 hours.

In one embodiment the invention relates to the method of treatment described above, characterised in that a compound of formula (I), or its polymorph, metabolite, hydrate, solvate, an individual optical isomer, mixtures of the individual enantiomers or racemates thereof, or a pharmaceutically acceptable salt thereof, is administered intermittent or in a daily dosage such that the plasma level of the active substance preferably lies between 10 and 5000 nM for at least 12 hours of the dosing interval.

However, it may optionally be necessary to deviate from the amounts specified, depending on the body weight or method of administration, the individual response to the medication, the nature of the formulation used and the time or interval over which it is administered. Thus, in some cases, it may be sufficient to use less than the minimum quantity specified above, while in other cases the upper limit specified will have to be exceeded. When large amounts are administered it may be advisable to spread them over the day in a number of single doses.

A compound of formula (I), its tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts, solvates, hydrates, polymorphs, physiologically functional derivatives or prodrugs thereof, may be used in monotherapy or combined with other active substances according to the invention, optionally also in conjunction with other pharmacologically active substances.

Pharmaceutical Formulations:

Suitable pharmaceutical preparations for the use in accordance with the invention include, for example, tablets, capsules, suppositories, solutions, and particularly solutions for injection (s.c., i.v., i.m.) and infusion, syrups, emulsions or dispersible powders. The amount of pharmaceutically active compound in each case should be in the range from 0.1-90 wt. %, preferably 0.5-50 wt. % of the total composition, i.e. in amounts which are sufficient to achieve the dosage range given below. The doses specified may, if necessary, be given several times a day.

Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharin, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions for injection and infusion are prepared in the usual way, e.g. with the addition of preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, optionally using emulsifiers and/or dispersants, while if water is used as the

diluent organic solvents may optionally be used as solubilisers or auxiliary solvents, and transferred into injection vials or ampoules or infusion bottles.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

Suitable excipients may be, for example, water, pharmaceutically acceptable organic solvents, such as paraffins (e.g. petroleum fractions), oils of vegetable origin (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolin, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silica and silicates), sugar (e.g. glucose, lactose and dextrose), emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

The preparations are administered in the usual way, preferably by oral or transdermal route, particularly preferably by oral route. When administered orally the tablets may, of course, contain additives, such as e.g. sodium citrate, calcium carbonate and dicalcium phosphate together with various additives, such as starch, preferably potato starch, gelatine and the like, in addition to the abovementioned carriers. Lubricants such as magnesium stearate, sodium laurylsulphate and talc may also be used to form tablets. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the abovementioned excipients. For parenteral use, solutions of the active substances may be prepared using suitable liquid carrier materials.

The following Examples serve to illustrate the invention without restricting it:

Example 1

Molecular Potency and Selectivity of BIBW 2992 Compared to Prior Art Compounds

The data summarized in table 1 were obtained using standard in-solution kinase assays performed at saturating ATP concentrations measuring incorporation of phosphate into poly (GluTyr). The same conditions were used for the different compounds in any kinase assay for direct comparison. IC50 values were generated from 12-point dose-response curves run in triplicates.

TABLE 1

BIBW 2992 is a potent and selective dual inhibitor of the EGFR and HER2 kinases

Code	EGFR-Kinase [nM]	HER2 Kinase [nM]	β-InsR Kinase [nM]	VEGFR-2 Kinase [nM]	HGFR Kinase [nM]	c-src Kinase [nM]
gefitinib (ZD-1839)	3	1100	>100000	>100000	>100000	>100000
erlotinib (OSI-774)	2	238	>100000	>100000	>100000	>100000
canertinib (CI-1033)	0.3	30	>100000	24900	>100000	1480
lapatinib (GW-2016)	3	15	>100000	>100000	>20000	>20000
BIBW 2992	0.5	14	>100000	>100000	13000	>4000

Example 2

Inhibition of EGF-Induced EGFR, and Constitutive HER2 Receptor Phosphorylation by BIBW 2992, Compared to Prior Art Compounds

EC50 values were generated from 12-point dose-response curves. For receptor phosphorylation assays cells were pre-incubated for 1 h with test compound. Cells were then either stimulated with EGF (100 ng/ml for 20 min) or directly harvested and tested for pEGFR or pHER2 by ELISA. Propidium iodide based assays were used to assess the proliferation of BT-474 cells in vitro. The compounds were tested under conditions allowing direct direct comparison.

Dual EGFR/HER2 inhibition results in more potent inhibition of cellular proliferation

TABLE 2

Cellular potency of BIBW 2992

	Receptor Phosphorylation				
Compound	A431 EGFR-PO_4 EC_{50} [nM]	NIH3T3 HER2-PO_4 EC_{50} [nM]	N87 HER2-PO_4 EC_{50} [nM]	BT-474 HER2-PO_4 EC_{50} [nM]	Proliferation BT-474 EC_{50} [nM]
gefitinib (ZD-1839)	35	2300	541	3710	1070
erlotinib (OsI-774)	5	734	468	930	829
canertinib (CI-1033)	22	85	288	184	66
lapatinib (GW-2016)	105	171	101	99	52
BIBW 2992	13	71	48	35	12

Example 3

Induction of Apoptosis by BIBW 2992

NCI-N87 gastric cancer cells were treated in vitro with 250 nM BIBW 2992. At indicated time points cells were harvested and samples were analyzed for free nucleosomes (apoptosis hallmark) using the Cell death ELISA kit #1774425 from Roche Diagnostics. Results are shown in FIG. **1** (Appendix).

The following Examples show that once daily dosing of BIBW 2992 significantly inhibits, in a dose dependent manner, the growth of a variety of human tumor xenografts in nude mice:

Example 4

Effect of BIBW 2992 on the Growth of Preexisting HNSCC FaDu Xenografts

Mice carrying established tumors (50-100 mm3) were treated orally, once daily at indicated doses. On the last day of treatment plasma samples were collected and analyzed for compound levels. Results are shown in FIG. **2** (Appendix).

Example 5

Effect of BIBW 2992 on the Growth of MDA-MB-453 and SKOV-3 Xenografts

Mice carrying established tumors (50-100 mm3) were treated orally, once daily at indicated doses with the respective compounds. On the last day of treatment plasma samples were collected and analyzed for compound levels. Results are shown in FIG. **3** (Appendix).

Example 6

Effect of BIBW 2992 on the Growth of Large NCI-N87 Xenografts

Mice carrying established tumors (Panel A: 50-100 mm3; Panel B: 450 mm3) were treated once daily p.o. with BIBW 2992 or once weekly i.v. with Herceptin at indicated doses. Daily oral treatment with BIBW 2992 induces regression of NCI-N87 xenografts. Results are shown in FIG. **4** (Appendix).

Example 7

Pharmacodynamic Evaluation of BIBW 2992 in Several Xenograft Models

Mice carrying established tumors (50-100 mm^3), were treated orally, once daily at indicated doses with the respective compounds. On the last day of treatment plasma samples were collected and analyzed for compound levels.

Daily oral treatment with BIBW 2992 at a dose of 20 mg/kg results in full anti-tumor activity in various xenograft models. Results are summarized in table 3.

TABLE 3

Model	Dose [mg/kg/d]	T/C [%]	Cmax [nM]	AUC [nM*h]
A431	30	2	587	4007
A431	20	2	285	3198
SKOV-3	20	3	236	2156
MDA-453	20	3	83	972
N87	20	4	80	1075
SKOV-3	15	13	83	589
N87	10	64	66	445
A431	10	80	87	382
A431	3	100	8	21

The T/C (Treated/Control) value corresponds to a % of control value:
median value in the treated group in relation to median value of tumor size in the control group (usually N=10) at the end of the experiment, set to 100% (e.g.: a median value in the treated group of 200 mm^3 in relation to a median value in the control group of 1000 mm^3 results a T/C value of 20%).

Example 8

Response of Patients Treated with BIBW2992

(a) One female patient with metastatic adenocarcinoma of the lung (NSCLC) treated with BIBW2992 MA2 at 10 mg daily (dose refers to the base form; continuous administration schedule) had a confirmed partial response after two months of treatment. The pulmonary lesions have clearly shrunk by >35%, confirmed with a repeat CT scan in 4 weeks. CT scans done in regular intervals confirm the continuation of the partial response. The patient treated developed brain metastases on treatment and increasing the dose of BIBW2992 to 40 mg daily has led to a response in her cerebral disease. This patient remains on treatment 23 months after starting BIBW 2992. This patient's tumour cells have a complex heterozygous EGFR mutation including a deletion and missense mutations of 4-amino acids in the kinase domain, but a wildtype HER2 domain.

(b) Another female patient with non-small cell lung cancer, pleural tumours and mediastinal lymph nodes treated with BIBW2992 MA2 also treated in a continuous dosing schedule at 40 mg daily did develop a partial response as measured by a CT scan after two months of treatment. Five target lesions had been identified; the sum thereof has gone down from 7.3 to 2.6 cm, a decrease of 65%. The patient remains in partial response 14 months after starting treatment with BIBW 2992. An in-frame deletion of 5 amino acids in the same region of the kinase domain has been detected in this patient.

(c) Using a 14 day on 14 day off schedule 2 patients with parotid tumors, one patient with esophageal cancer, one patient with colorectal cancer, one patient with breast cancer, one patient with thyroid cancer and one patient with other endocrine cancer have had stable disease for at least 6 months and have been treated for more than 6 months.

(d) In a continuous dosing schedule and in addition to the above mentioned non-small cell lung cancer patients with partial remissions, a patient with thymic cancer (40 mg daily) and a patient with ovarian cancer (20 mg daily) have had stable disease for at least six months.

(e) In a combined treatment schedule with docetaxel (given every 3 weeks) and BIBW 2992 given for 3 days after the administration of docetaxel one patient had a complete response (breast cancer) and one had partial response (oesophageal).

(f) In a combined treatment schedule with docetaxel (given every 3 weeks) and BIBW 2992 given for 20 or 13 days after the administration of docetaxel, two patients had a partial responses (ovarian and non-small cell lung cancer).

Example 9

Coated Immediate-Release Tablets Containing 75 mg of Active Substance by Dry-Granulation Process

Composition:

1 tablet contains:

active substance	75.0 mg
calcium phosphate anhydrous	108.0 mg
corn starch	35.5 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	1.5 mg
hydroxypropylmethylcellulose	7.5 mg
polyethylene glycol	1.0 mg
polydextrose	5.0 mg
talc	1.0 mg
pigments	0.5 mg
water (volatile)	
	245.0 mg

Preparation:

The active substance is mixed with calcium phosphate, corn starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. Ribbons are produced in a roller-compactor and these are then rubbed through a screen with a mesh size of 1.5 mm using a suitable machine and mixed with the rest of the magnesium stearate. This granulate is compressed in a tablet-making machine to form tablets of the desired shape.

Weight of core: 230 mg

Tablet shape: 9 mm round, bi-convex

The tablet cores are subsequently coated with an aqueous film-coat consisting essentially of hydroxypropylmethylcellulose, polyethylene glycol, polydextrose, talc and pigments.

Weight of coated tablet: 245 mg.

Example 10

Extended-Release Tablets Containing 100 mg of Active Substance by Organic Granulation Granulation Process

1 tablet contains:

active substance	100.0 mg
lactose	34.0 mg
hydroxypropylmethylcellulose	80 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	2.0 mg
ethanol (volatile)	
	220.0 mg

Preparation:

The active substance, lactose and hydroxypropylmethylcellulose are mixed together and uniformly moistened with solution of the polyvinylpyrrolidone in ethanol. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier at 50° C. it is screened again (1.5 mm mesh size) and the lubricant is added. The final blend is compressed to form tablets.

Weight of tablet: 220 mg

Tablet shape: 10 mm, flat-faced, with bevelled edges.

Example 11

Tablets Containing 150 mg of Active Substance by Aqueous Granulation Process

1 tablet contains:

active substance	150.0 mg
powdered lactose	98.0 mg
corn starch	40.0 mg
colloidal silica	1.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	1.0 mg
	300.0 mg

Preparation:

The active substance mixed with lactose, corn starch is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm. The granules, dried at 45° C., are passed through the same screen again and mixed with the specified amount of magnesium stearate and colloidal silica. Tablets are pressed from thefinal blend.

Weight of tablet: 300 mg

Tablet shape: 14 mm×6.8 mm, oblong biconvex with embossement

Example 12

Hard Capsules Containing 150 mg of Active Substance in Granules

Composition:

1 capsule contains:

active substance	150.0 mg
microcrystalline cellulose	80.0 mg
lactose (spray-dried)	87.0 mg
colloidal silica	10.0 mg
	320.0 mg

Preparation:

The active substance is mixed with the excipients in a high-shear mixer, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatin capsules.

Capsule filling: 320 mg

Capsuleshape: size 1, opaque hard capsule.

Example 13

Hard Capsules Containing 150 mg of Active Substance as a Liquid Fill

Composition:

1 capsule contains:

active substance	150.0 mg
groundnut oil	300.0 mg
colloidal silica	10.0 mg
	460.0 mg

Preparation:

The active substance is dissolved in the excipient inside a homogenizer and the colloidal silica is added for adjustment of viscosity. The finished mixture is filled into size 1 hard gelatin capsules.

Capsule filling: 460 mg

Capsuleshape: size 0, opaque hard capsules.

Example 14

Suppositories Containing 150 mg of Active Substance

Composition:

1 suppository contains:

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	840.0 mg
	2,000.0 mg

Preparation:

After the suppository mass has been melted the active substance is homogeneously suspended therein and the melt is poured into chilled moulds.

Example 15

Suspension Containing 50 mg of Active Substance

Composition:

100 ml of suspension contain:

active substance	1.00 g
carboxymethylcellulose-Na-salt	0.10 g
methyl p-hydroxybenzoate	0.05 g
propyl p-hydroxybenzoate	0.01 g
glucose	10.00 g
glycerol	5.00 g
70% sorbitol solution	20.00 g
flavouring	0.30 g
dist. water	ad 100.0 ml

Preparation:

The distilled water is heated to 70° C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt of carboxymethylcellulose are dissolved therein with stirring. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stilling. After the sugar, the sorbitol solution and the flavouring have been added and dissolved, the suspension is evacuated with stirring to eliminate air.

5 ml of suspension contain 50 mg of active substance.

Example 16

Ampoules Containing 10 mg Active Substance

Composition:

1 ampoule contains:

active substance	10.0 mg
0.01N hydrochloric acid.	q.s
sodium chloride	q.s.
double-distilled water	ad 2.0 ml

Preparation:

The active substance is dissolved in the requisite amount of 0.01 N HCl, made isotonic with sodium chloride, filtered sterile and transferred into 2 ml ampoules with subsequent steam sterilization.

Example 17

Ampoules Containing 50 mg of Active Substance

Composition:

1 ampoule contains:

active substance	50.0 mg
0.01N hydrochloric acid	q.s.
sodium chloride	q.s.
double-distilled water	ad 10.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with sodium chloride, filtered sterile and transferred into 10 ml ampoules with subsequent steam sterilization.

Example 18

Capsules for Powder Inhalation Containing 5 mg of Active Substance

Composition:

1 capsule contains:

active substance	5.0 mg
lactose for inhalation	15.0 mg
	20.0 mg

Preparation:

The active substance is mixed with lactose for inhalation. The mixture is packed into capsules in a capsule-making machine (weight of the empty capsule approx. 50 mg). weight of capsule: 70.0 mg size of capsule 3

Example 19

Solution for Inhalation for Hand-Held Nebulisers Containing 2.5 mg Active Substance

Composition:

1 spray contains:

active substance	2.500 mg
benzalkonium chloride	0.001 mg
1N hydrochloric acid q.s.	2.500 mg
ethanol/water (50/50 m/m)	ad 15.000 mg

Preparation:

The active substance and benzalkonium chloride are dissolved in ethanol/water (50/50). The pH of the solution is adjusted with 1N hydrochloric acid. The resulting solution is filtered sterile and transferred into suitable containers for use in hand-held nebulisers (cartridges).

Contents of the container: 4.5 g

The invention claimed is:

1. A method for treating metastatic non-small cell lung cancer (NSCLC) of squamous histology in a second line patient having failed at least one prior chemotherapy regimen, the method comprising administering to said patient a therapeutically effective amount of the compound 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, or a physiologically acceptable salt thereof.

2. The method of claim **1**, wherein the 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, or a physiologically acceptable salt thereof, is used in monotherapy or in combination with another anti-tumour therapeutic agent.

3. The method of claim **2**, wherein the other anti-tumour therapeutic agent is selected from the group consisting topoisomerase inhibitors, mitosis inhibitors, compounds which interact with nucleic acids, hormone antagonists, inhibitors of metabolic processes, cytokines, and antibodies.

4. The method of claim **2**, wherein the other anti-tumour therapeutic agent is cis-platinum.

5. The method of claim **2**, wherein the compound is 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate.

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